



Dr. dr. Dwiana Ocviyanti, SpOG(K)

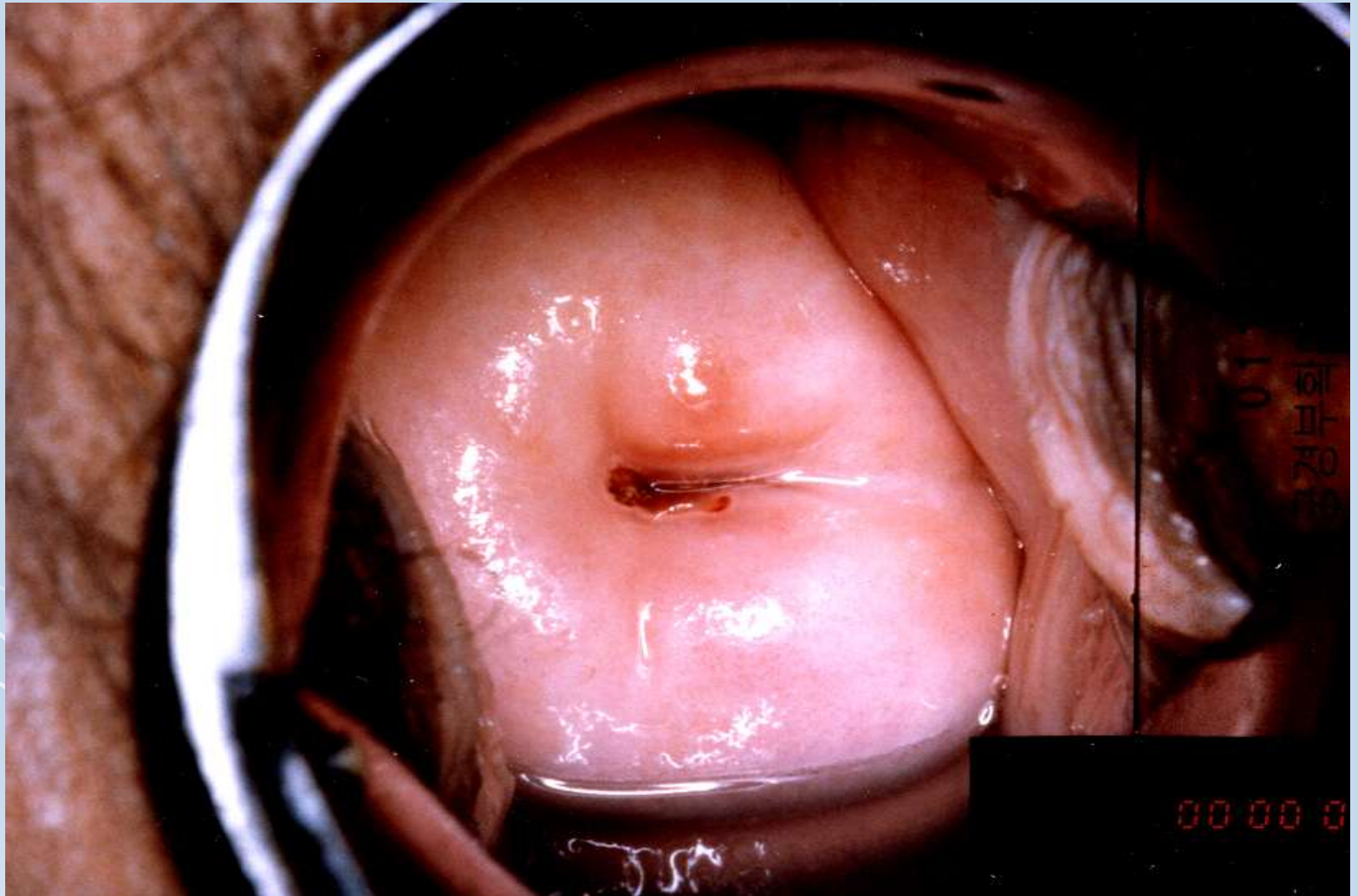
- Lahir di Bandung, 4 Oktober 1961
- Staf pengajar
Departemen Obstetri dan Ginekologi
Fakultas Kedokteran Universitas Indonesia/
Rumah Sakit dr Cipto Mangunkusumo, Jakarta

Riwayat Pendidikan

- Program S1- pendidikan Dokter di Fakultas Kedokteran Universitas Indonesia, Jakarta, lulus Agustus 1986
- Program S2- pendidikan Dokter Spesialis Obstetri dan Ginekologi Fakultas Kedokteran Universitas Indonesia, Jakarta, lulus Agustus 1995
- Program S3- pendidikan Dokter Epidemiologi , peminatan Epidemiologi Klinik FKM Universitas Indonesia, Jakarta, lulus Juni 2006
- Program Konsultan Obstetri dan Ginekologi Sosial, Kolegium Obstetri dan Ginekologi, selesai Juli 2006

VAKSIN HPV SEBAGAI PENCEGAHAN PRIMER KANKER LEHER RAHIM

Dr.dr.Dwiana Ocviyanti, SpOG(K)



Apa penyebab Kanker Leher Rahim?

- Infeksi yang menetap (persisten) dari Virus HPV yang onkogenik pada perempuan



Cervical Cancer Is Essentially Caused by Oncogenic HPV

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.¹
 - **HPV is a main cause of cervical cancer.**²
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = **99.7%.**²
 - Tissue samples were analyzed for HPV DNA by 3 different polymerase chain reaction (PCR)–based assays, and the presence of malignant cells was confirmed in adjacent tissue sections.²

HPV

Nonenveloped double-stranded DNA virus¹



- **>120 types identified²**
- **~30–40 anogenital types^{2,3}**
 - ~15–20 oncogenic types^{*,2,3}**
 - **HPV 16 and HPV 18 types account for the majority of worldwide cervical cancers.⁴**
 - ~15-20 nononcogenic^{**} types**
 - HPV 6 and 11 types are most often associated with external anogenital warts.³**

*High risk; ** Low risk

1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229.

2. Schiffman M, Castle PE. *Arch Pathol Lab Med.* 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis.* 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer.* 2004;111:278–285.

Clinical Significance of Genital HPV Types

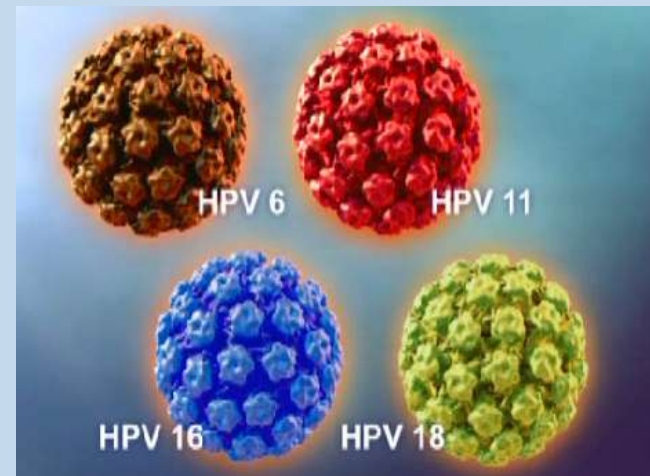
Although there are over 30 genital HPV types, 4 types cause the great majority of clinical HPV disease

HPV 16 and 18

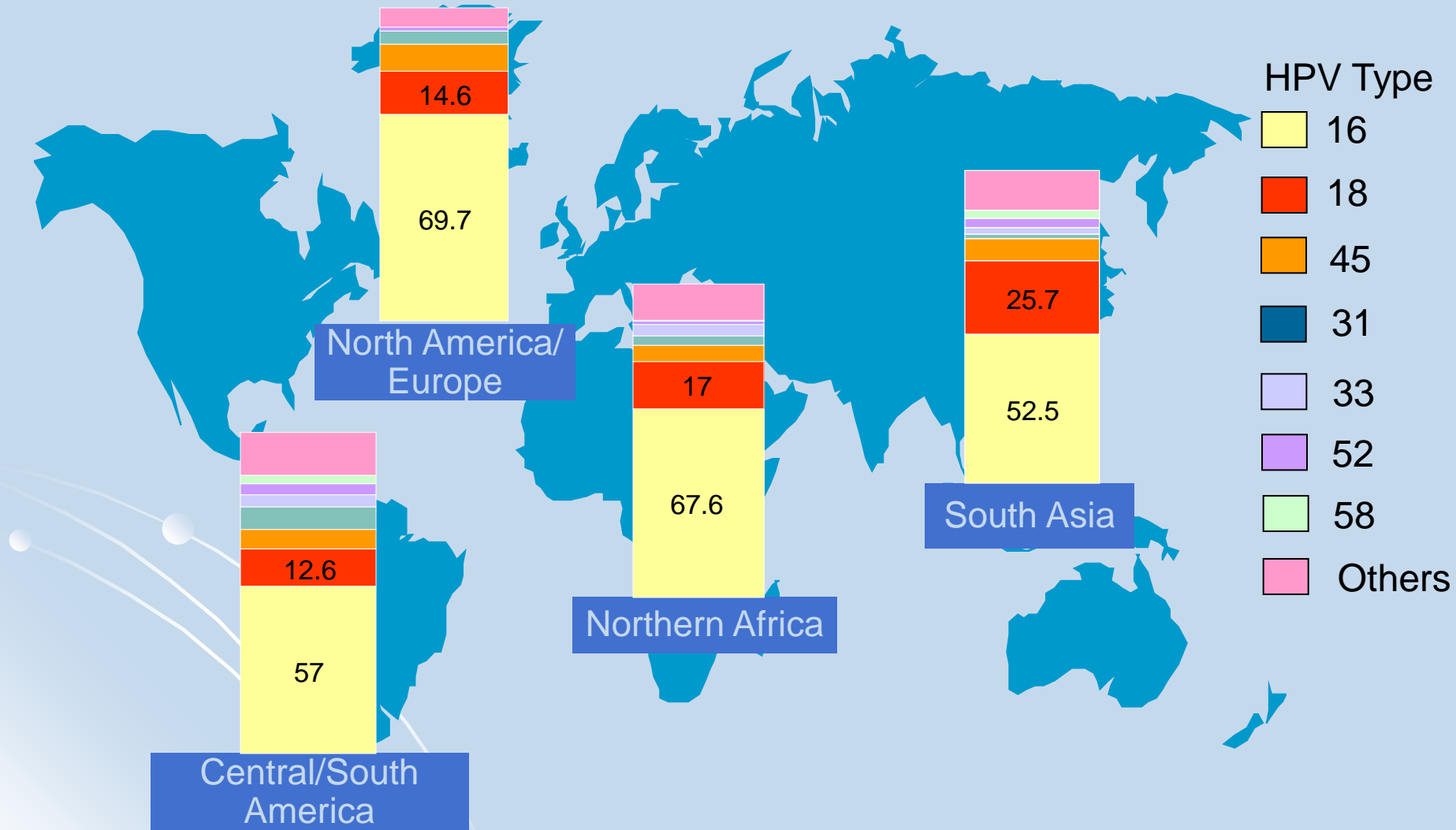
- cause ~25% of low-grade (CIN 1) lesions
- cause ~70% of cervical precancers (CIN 2/3) and cancers
 - HPV 16 → squamous cell carcinoma
 - HPV 18 → adenocarcinoma

HPV 6 and 11

- cause ~10-15% of low-grade (CIN 1) lesions
- cause over 90% of genital warts



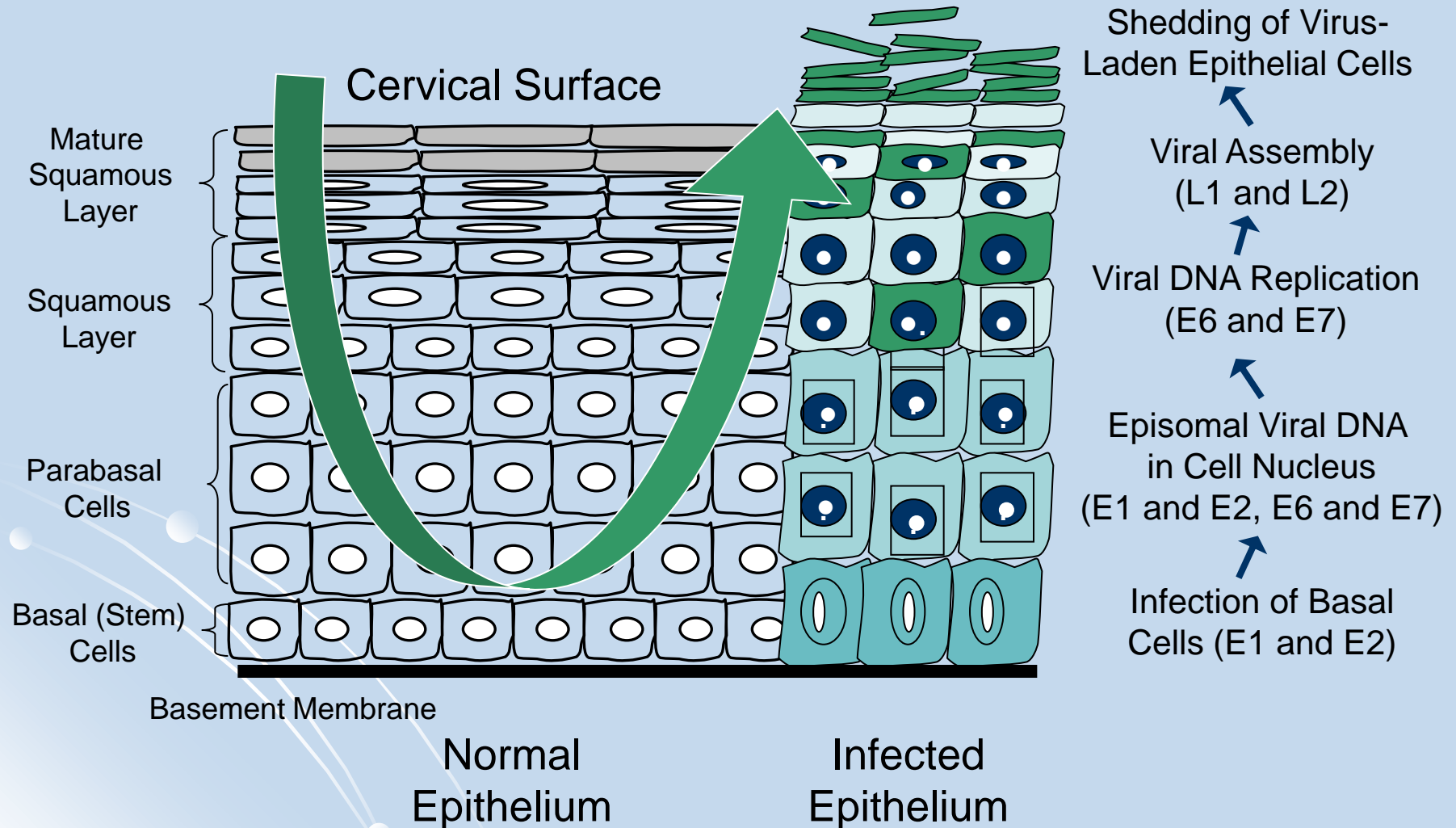
Worldwide Prevalence of HPV Types in Cervical Cancer*,1



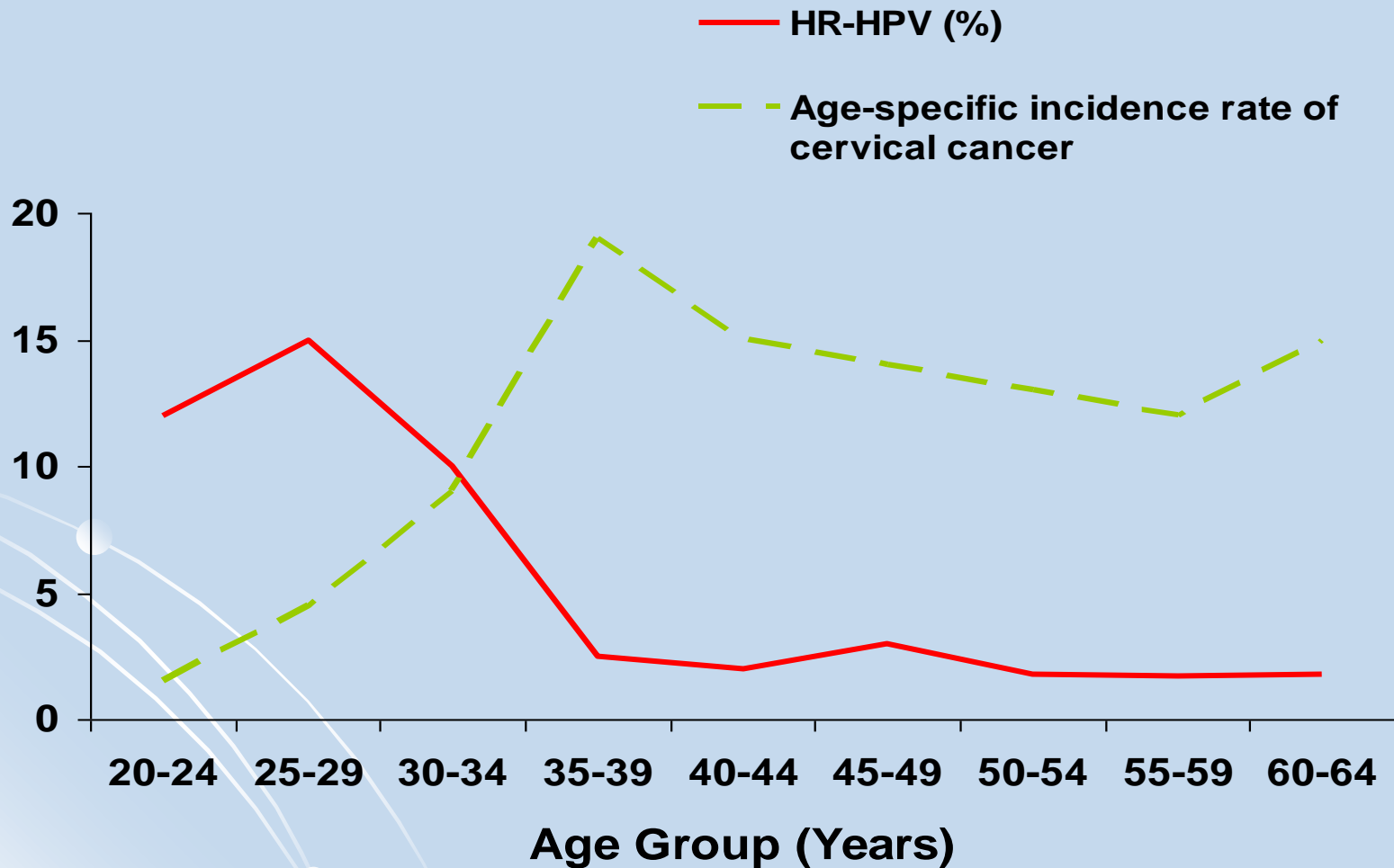
*A pooled analysis and multicenter case control study (N = 3607)

1. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

HPV Infection and Life Cycle¹



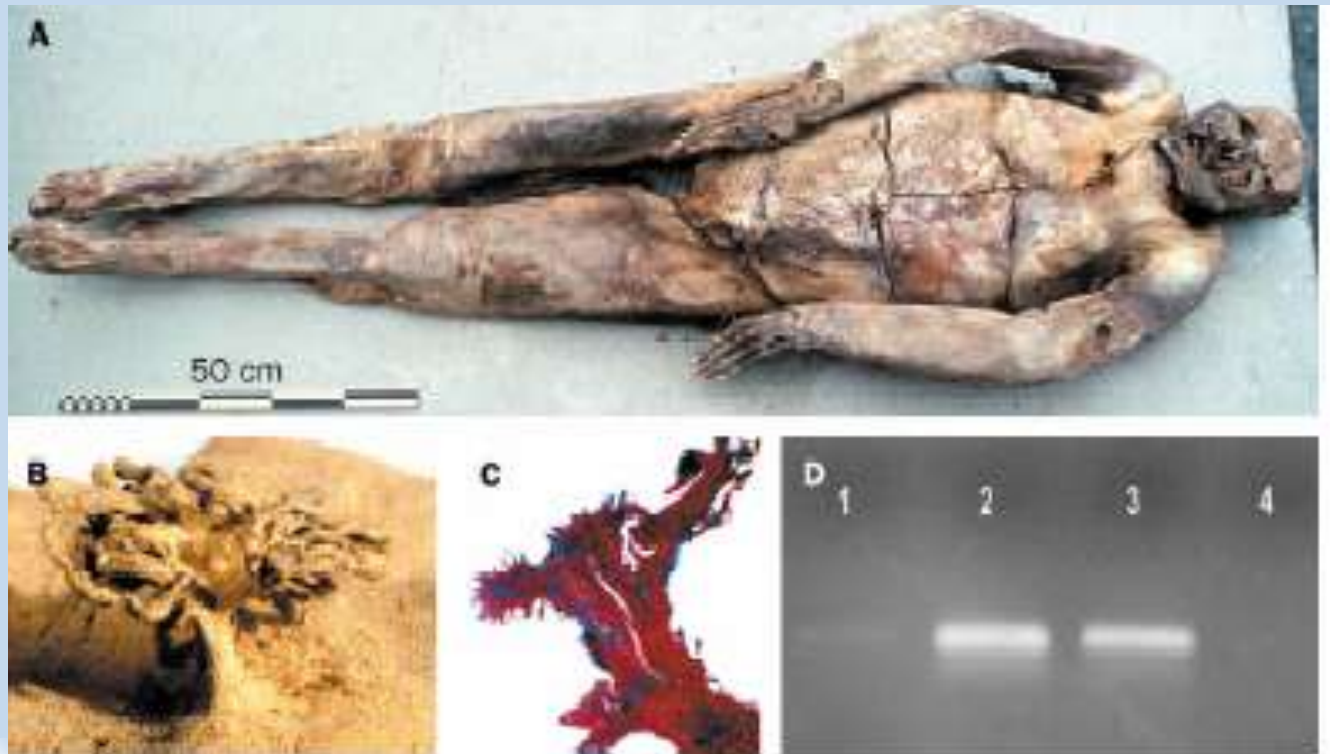
Age-Specific Incidence Rates of HPV Infection & Cervical Cancer



Bagaimana seorang perempuan dapat terinfeksi virus HPV?

- Infeksi HPV merupakan infeksi yang umum terjadi
- Penularan utama HPV yang menyebabkan kanker leher rahim adalah melalui kontak seksual

A Bit of History

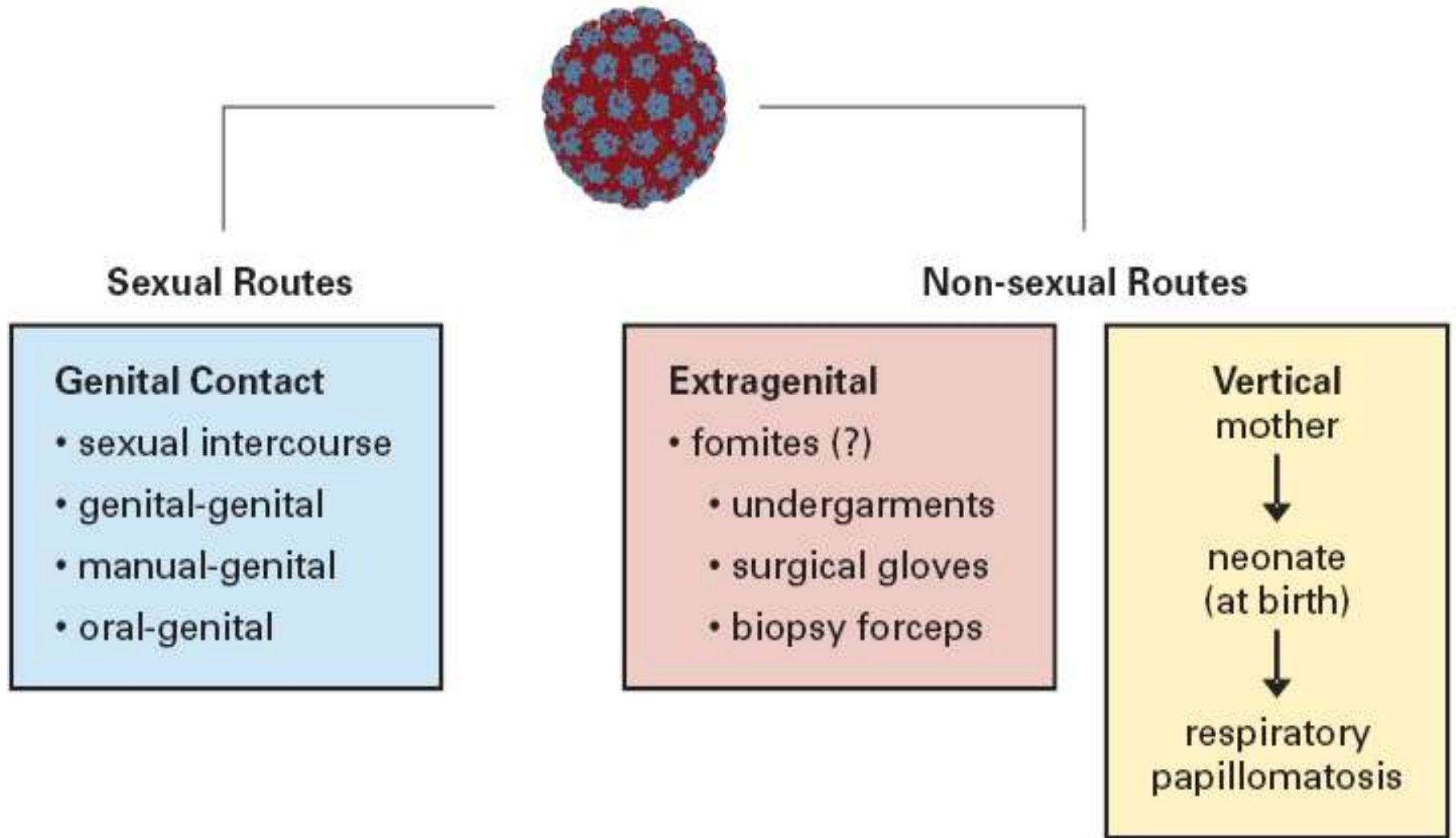


Identification of HPV infection in mummy of Mary of Aragon (1568)

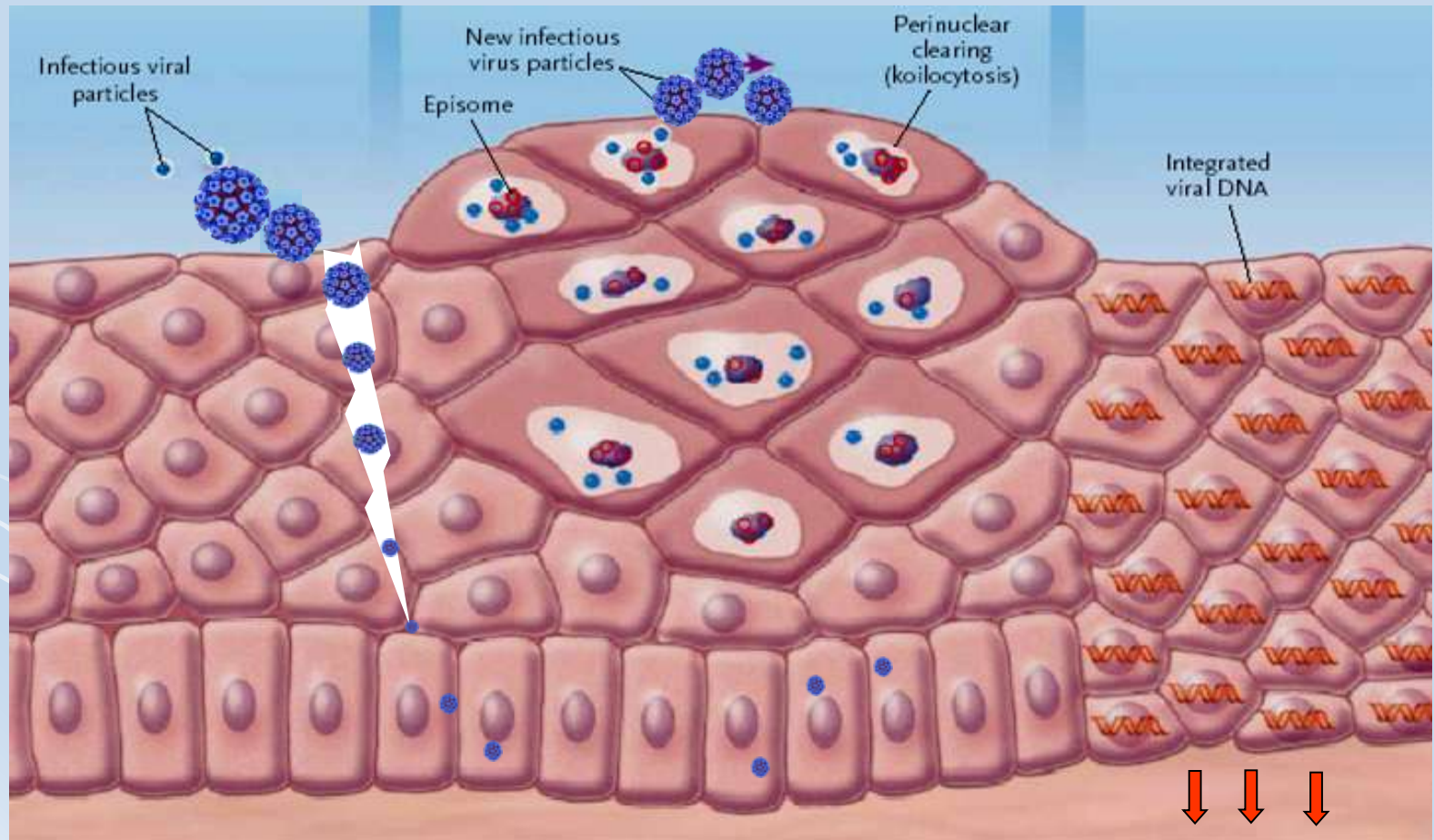
(A) Artificial mummy with asymmetrical swelling of lower limbs: left leg more voluminous than right one, with deep marks of knee sock laces, probably caused by local venous stasis and oedema at moment of death. (B) Pedunculated, branching skin tumour (magnification $\times 7$). (C) Section of papillary tumour, with peduncule and dilated vessels ($\times 10$). (D) PCR products of HPV from mummy DNA: lane 1=PCR product of HPV from mummy sample (141 bp); lane 2=enriched PCR of HPV; lane 3=positive control; lane 4=blank sample.

HPV 18 DNA isolated from a 16th century mummy by the use of PCR. The mummy was Mary of Aragon (1503-1568) who also showed signs of syphilis.

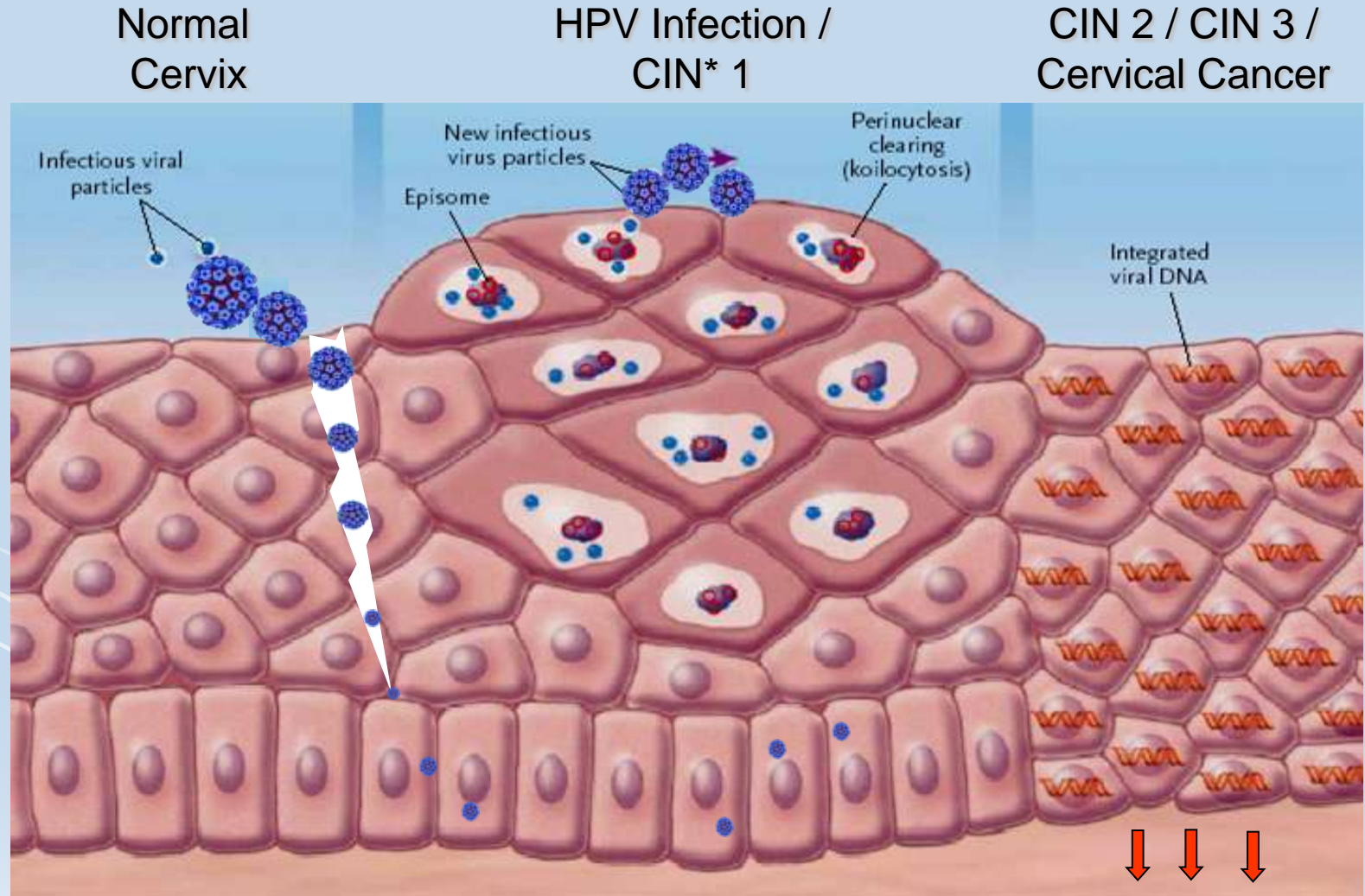
Routes of HPV Transmission



Bagaimana Virus HPV masuk ke dalam tubuh dan menyebabkan Kanker Leher Rahim



Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection¹

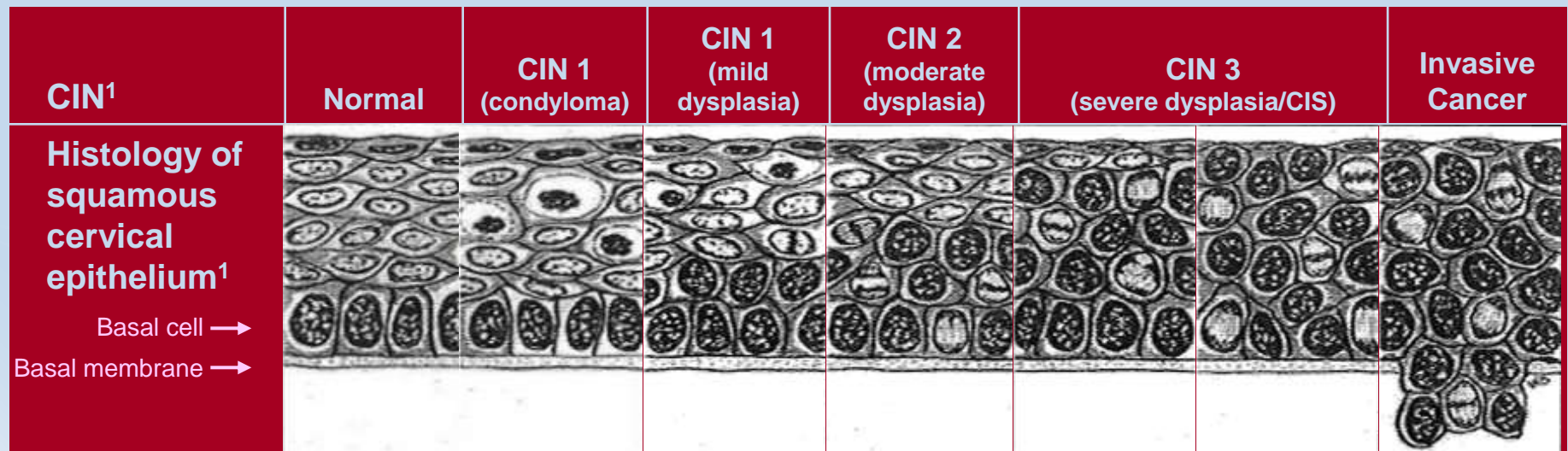


*CIN = cervical intraepithelial neoplasia

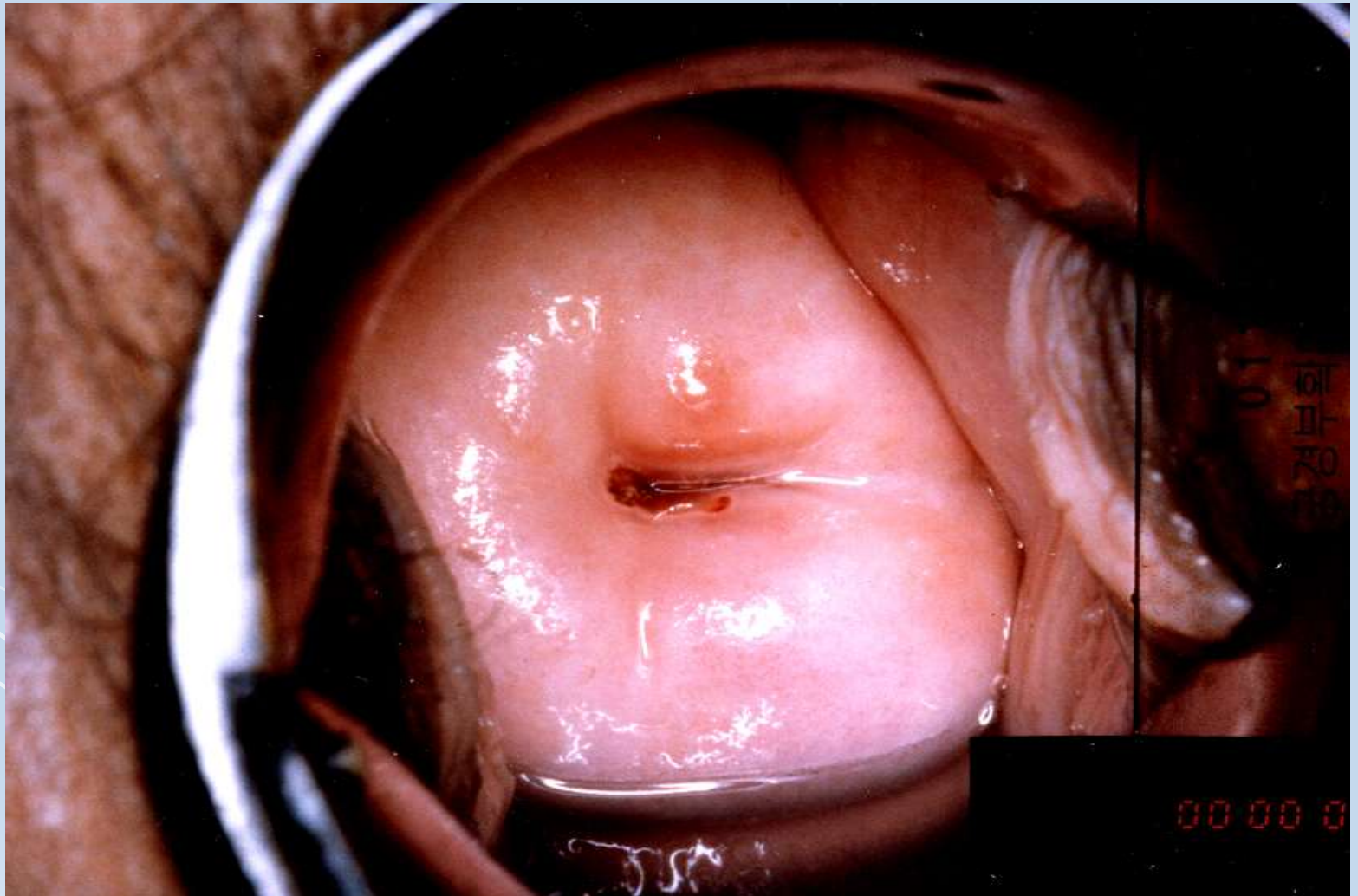
1. Adapted from Goodman A, Wilbur DC. *N Engl J Med.* 2003;349:1555–1564. Copyright © 2003 Massachusetts Medical Society. All rights reserved. Adapted with permission.

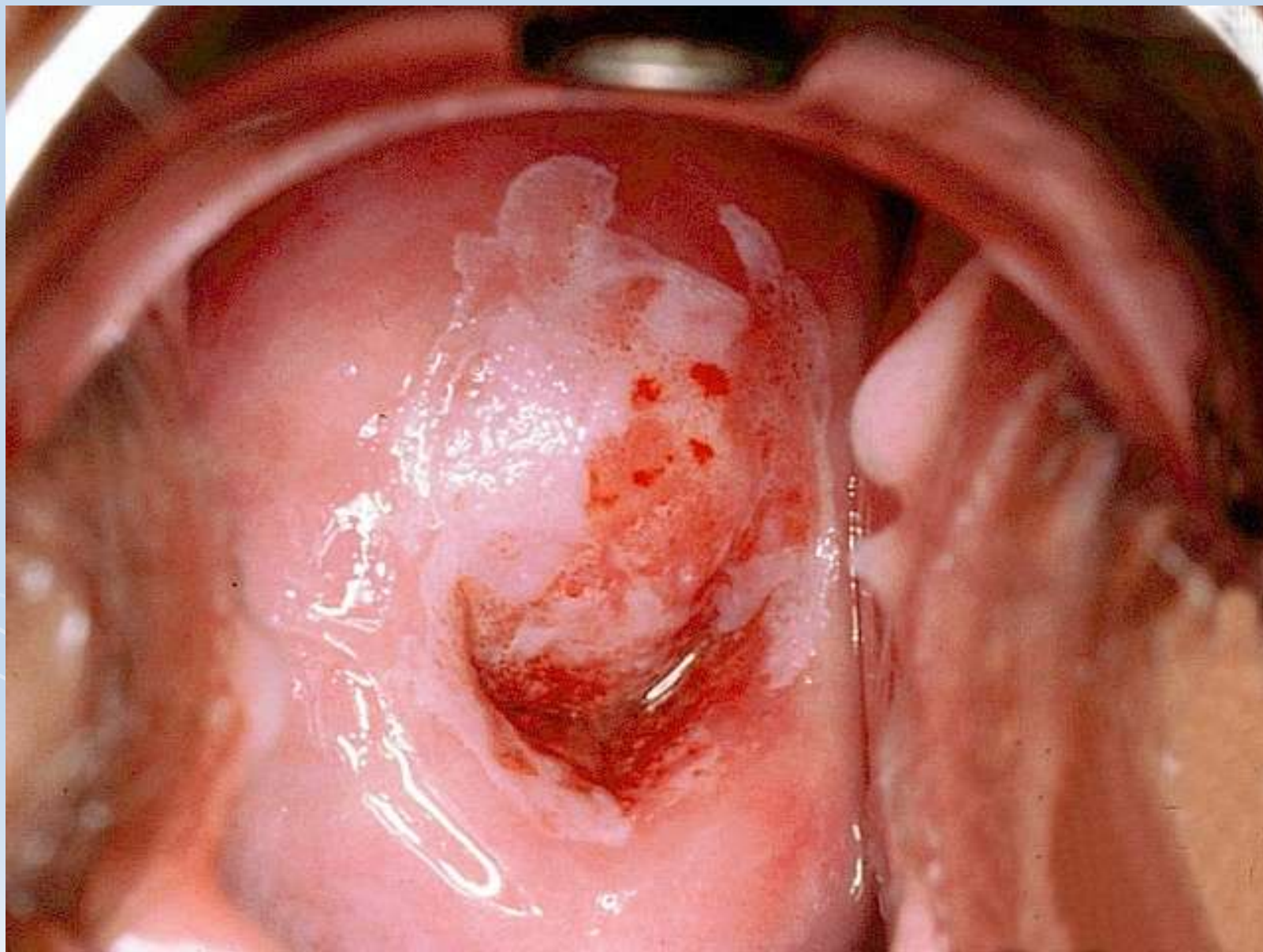
Classification of Histological Findings: Cervical Intraepithelial Neoplasia

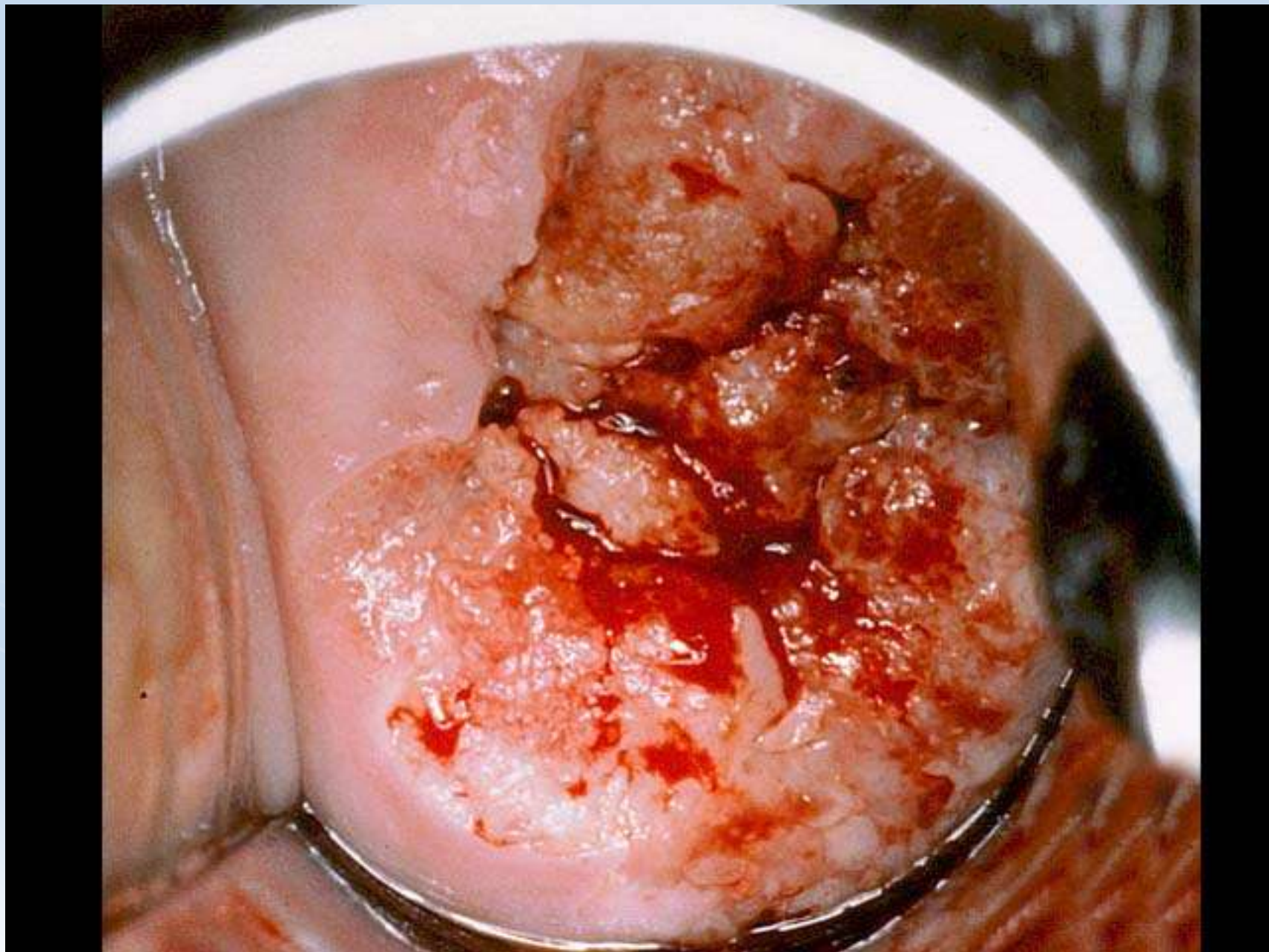
- Cervical intraepithelial neoplasia (CIN)¹
 - CIN 1: Mild dysplasia; includes condyloma (anogenital warts)
 - CIN 2: Moderate dysplasia
 - CIN 3: Severe dysplasia; includes CIS



- CIN caused by HPV can clear without treatment.²

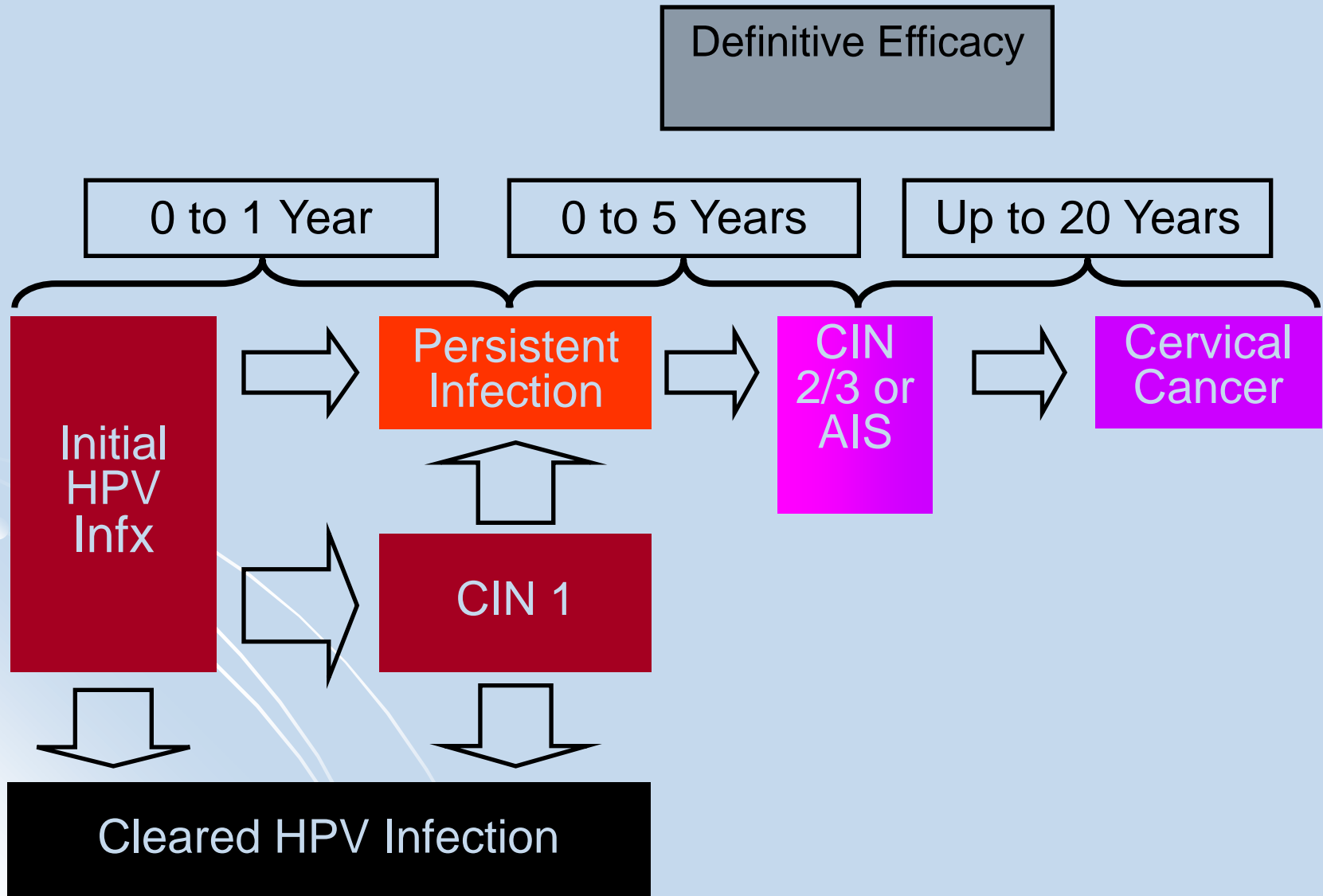






CIN 2/3 and AIS

Established Surrogate Markers for Cervical Cancer



Fakta tentang Kanker Leher Rahim

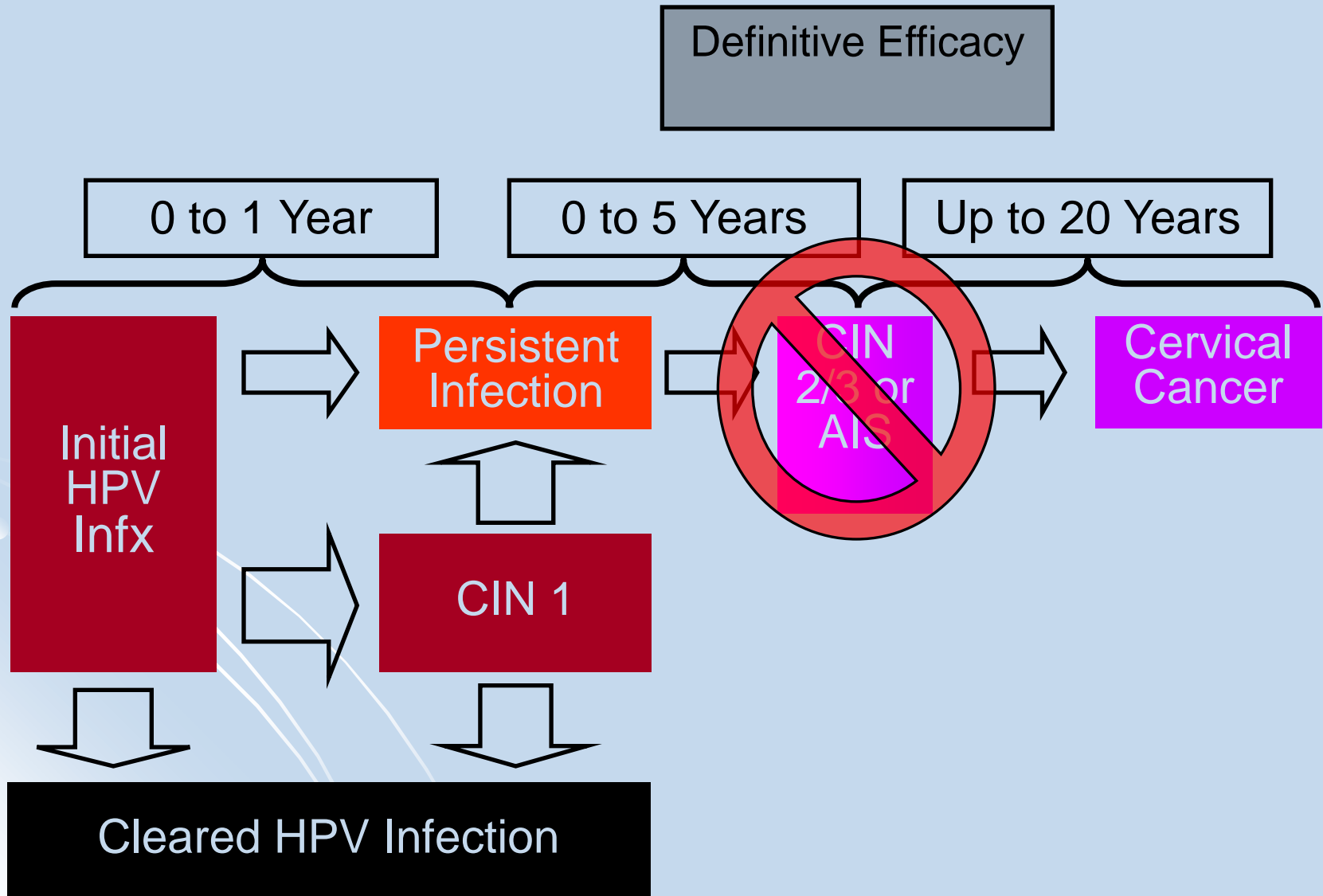
- Disebabkan oleh virus HPV (*human papilloma virus*)
- Hanya diderita oleh perempuan yang sudah pernah melakukan hubungan seksual
- Perkembangan penyakit membutuhkan waktu lama , antara 10-20 tahun
- Pada fase prakanker dan pada stadium awal tidak menimbulkan gejala
- Dapat dicegah!

Vaksinasi HPV

- Dapat mencegah infeksi HPV tipe 16 dan 18 yang diketahui menyebabkan hampir 70 persen kanker serviks
- Saat ini ada dua jenis: bivalen (HPV 16,18) dan kuadrivalen (HPV 6,11,16,18)
- Vaksinasi dalam bentuk suntikan sebanyak 3 kali (bulan ke 0, 1 at 2, 6)
- Dapat diberikan mulai usia 9 hingga 45 tahun

CIN 2/3 and AIS

Established Surrogate Markers for Cervical Cancer



Clinical Program for Quadrivalent HPV vaccine

Combined Efficacy Analysis

Ph II–P005 (N=2392)¹
Proof of Principle
16- to 23-year-old women

Ph II–P007 (N=1158)²
Dose-ranging
16- to 23-year-old women

Yr 5 Immune Memory
Evaluation

- > 26,000 subjects enrolled
- Ethnically diverse
- 33 countries

Ph III–FUTURE I CIN/EGL (N=5455)³
16- to 24-year-old women

Ph III–FUTURE II CIN 2/3 (N=12,167)⁴
15- to 26-year-old women

Duration of Efficacy Registry Study
Nordic Region

Norwegian HPV Surveillance and
Disease Burden/Population Effectiveness Study

Ph III–P016, P018 (N=4836)
Safety/Immunogenicity
9- to 15-year-old boys and girls^{5,6}

Efficacy in women up to 45 years old⁶

Efficacy in 16- to 26-year-old men⁶

Jan 2003 Jan 2004 Jan 2005 Jan 2006 Jan 2007 Jan 2008 Jan 2009 Jan 2010

EGL = external genital lesions.

Prophylactic Efficacy: 100% Efficacious Against HPV 6/11/16/18-Related CIN¹

PPE Population

End Point By Lesion Type	Quadrivalent HPV vaccine Cases* (n=2240)	Placebo Cases* (n=2258)	Vaccine Efficacy	97.5% CI	P Value
HPV 6/11/16/18 CIN	0	37	100%	87–100	<0.001
CIN 1	0	25	100%	84–100	
CIN 2 or worse	0	20	100%	80–100	

Per-protocol = received 3 doses of vaccine; no major protocol violations; HPV sero(-) at day 1 and HPV DNA(-) from day 1 to month 7; cases counted starting after month 7, and the follow-up was an average of 1.5 years postvaccination.

*Subjects are counted once per row, but may be counted in more than 1 row.

1. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Submitted. 2006.

Prophylactic Efficacy: 100% Efficacious Against HPV 6/11/16/18-Related VIN/VaIN and Genital Warts¹

PPE Population

End Point By Lesion Type	Quadrivalent HPV vaccine Cases* n=2261	Placebo Cases* n=2279	Vaccine Efficacy	97.5% CI	P Value
HPV 6/11/16/18 VIN/VaIN, genital warts	0	40	100%	88–100	<0.001
Genital warts	0	29	100%	86–100	
VIN 1 or VaIN 1	0	8	100%	41–100	
VIN 2/3 or VaIN 2/3	0	7	100%	30–100	

Per-protocol = received 3 doses of vaccine; no major protocol violations; HPV sero(-) at day 1 and HPV DNA(-) from day 1 to month 7; cases counted starting after month 7, and the follow-up was an average of 1.5 years postvaccination.

*Subjects are counted once per row, but may be counted in more than 1 row.

1. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Submitted. 2006.

Prophylactic Efficacy Against HPV 6/11/16/18-Related Lesions¹

PPE-Combined Population

End Point: HPV 6/11/16/18-Related	Quadrivalent HPV vaccine Cases	Placebo Cases	Vaccine Efficacy	95% CI
	n=7858	n=7861		
CIN or AIS	4	83	95%	87–99

End Point: HPV 6/11/16/18-Related	Quadrivalent HPV vaccine Cases*	Placebo Cases*	Vaccine Efficacy	95% CI
	n=7897	n=7899		
Genital warts	1	91	99%	94–100

- The efficacy of HPV vaccine against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100%.

*Subjects are counted once per row but may be counted in more than 1 row.

Clinical trials in over 25,000 participants demonstrated 100% efficacy of our vaccine against pre-cancerous lesions

Our vaccine prevented 95-100% of HPV 16/18/6/11-related CIN, AIS or EGL in women not yet infected with either HPV 16, 18, 6, or 11 at baseline

Cervical Cancer	Vulvar/Vaginal Cancer
100% Effective	
Against Human Papillomavirus 16- and 18-related CIN 2/3 or AIS	Against Human Papillomavirus 16- and 18-related VIN 2/3 or VaIN 2/3

Cervical Dysplasia	Genital Warts
95% Effective	99% Effective
Against Human Papillomavirus 6-, 11-, 16- and 18-related CIN (CIN 1, CIN 2/3) or AIS	Against Human Papillomavirus 6-, 11-, 16- and 18-related genital lesions (genital warts, VIN, VaIN)

Participants (women 16 to 26) in 33 countries around the world

¹Per protocol populations

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ; EGL = external genital lesions; VIN/ VaIN = Vulva/ Vaginal intraepithelial neoplasia

Vaksin HPV Quadrivalen

- Mencegah infeksi HPV 16 dan 18 – mencegah kanker serviks
- Mencegah infeksi HPV 6 dan 11 – mencegah kutil kemaluan (kondiloma) termasuk kutil pada tenggorokan bayi (papilloma laring)
- Kutil yang disebabkan HPV – sulit untuk diterapi tuntas dan kerap berulang

Quadrivalent HPV L1 VLP Vaccine¹

- Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine
- VLPs manufactured in *Saccharomyces cerevisiae*
 - Yeast-derived vaccines given to millions of children and adults.
- Aluminum adjuvant 225 µg per dose
- 0.5 mL injection volume
- 3 doses within 6 months **(0,2 and 6)**
- Females 9–26 years old & males 9–15 years old

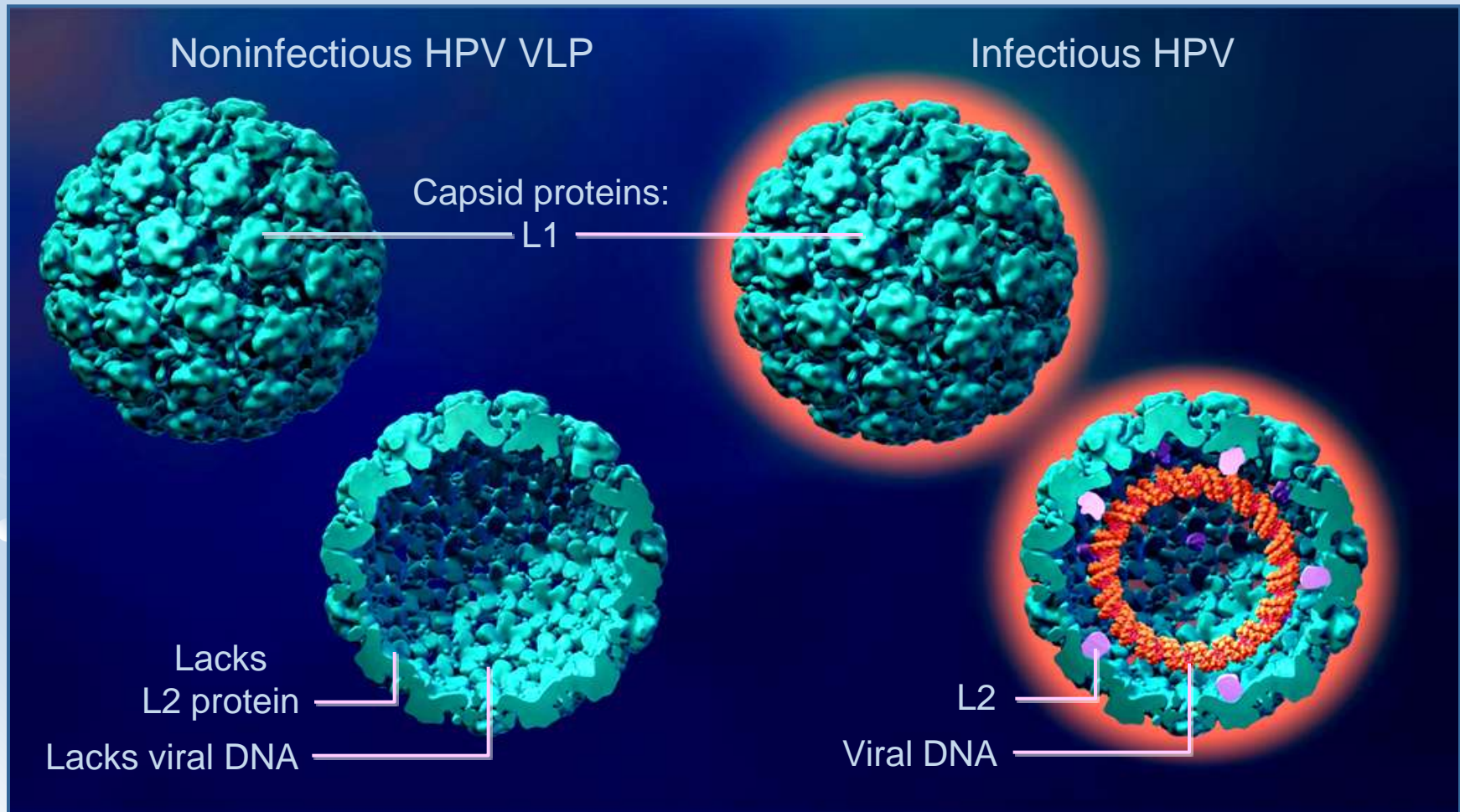


GARDASIL is a trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

*VLP = Virus-like particle.

1. Villa LL, Costa RL, Petta CA, et al. *Lancet Oncol.* 2005;6:271–278.

Structure of Human Papiloma Virus and GARDASIL (Virus Like Particle)



L1 VLPs Mimic the HPV Virion¹⁻⁴

1. Stanley M. *Vaccine*. 2006;24(Suppl 1):S16-S22.
2. Berzofsky JA, et al. *J Clin Invest*. 2004;114:450-462.
3. Baker TS, et al. *Biophys J*. 1991;60:1445-1456.
4. Chen XS, et al. *Mol Cell*. 2000;5:557-567.

Rationale for a Quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP Vaccine

- A prophylactic quadrivalent HPV (Types 6, 11, 16, and 18) vaccine is expected to substantially reduce the burden of HPV-related diseases.¹

Type	Women	Males
6/11	<ul style="list-style-type: none"> • >90% of genital warts^{2a} • ~10% of low-grade cervical lesions^{3b} 	<ul style="list-style-type: none"> • >90% of genital warts^{2a} • Transmission to women⁹
16/18	<ul style="list-style-type: none"> • ~25% of low-grade cervical lesions^{3b} • ~50% of high-grade cervical lesions^{4c} • ~70% of cervical cancer^{3b,5d,6e} • ~70% of other genital cancers^{7f,8g} 	<ul style="list-style-type: none"> • ~60% of anal cancer^{10h} • Transmission to women⁹

^a Study of 63 cases of condyloma.

^b Meta-analysis of 55 studies.

^c Meta-analysis of 53 studies.

^d Pooled analysis of 11 case-controlled studies involving 1918 women with cervical cancer.

^e Meta-analysis of 85 studies.

^f Case-controlled study of 156 women with vaginal cancer.

^g Study of 81 cases of non-cervical anogenital cancers.

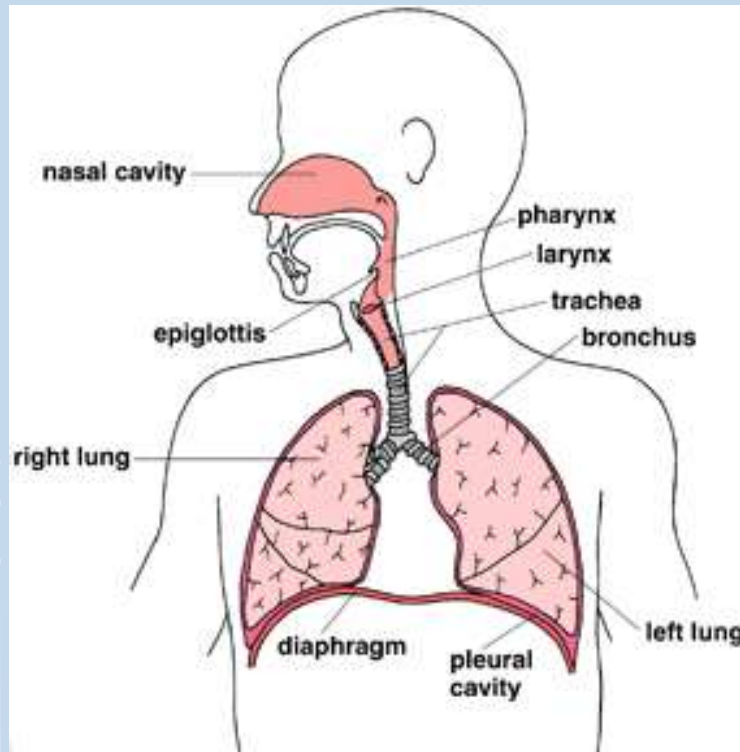
^h Study of 388 patients with anal cancer.

1. Franco EL, Harper DM. *Vaccine*. 2005;23:2388–2394. 2. Gissman L, Wolnik L, Ikenberg H, et al. *Proc Natl Acad Sci USA*. 1983;80:560–563. 3. Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1157–1164. 4. Clifford GM, Smith JS, Aguado T, Franceschi S. *Br J Cancer*. 2003;89:101–105. 5. Muñoz N, Bosch FX, de Sanjosé S, et al. *N Engl J Med*. 2003;348:518–527. 6. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. *Br J Cancer*. 2003;88:63–73. 7. Daling JR, Madeleine MM, Schwartz SM, et al. *Gynecol Oncol*. 2002;84:263–270. 8. Bjorge T, Dillner J, Anttila T, et al. *BMJ*. 1997;315:646–649. 9. Castellsagué X, Bosch FX, Muñoz N. *Salud Publica Mex*. 2003;45(suppl 3):S345–353. 10. Frisch M, Glimelius B, van den Brule AJC, et al. *N Engl J Med*. 1997;337:1350–1358.

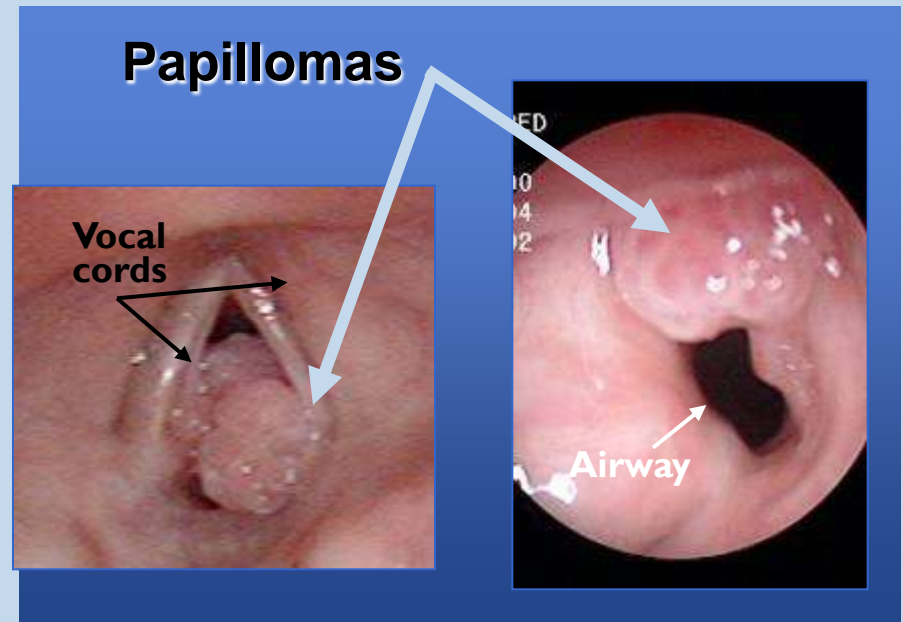
Kondiloma (Kutil Kelamin)



Kutil Saluran Napas Bayi/Anak (Papilloma laring)



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Photos courtesy of Craig S. Derkay, MD
Eastern Virginia Medical School

Quadrivalent HPV vaccine: Durable Protection Through 5 Years

PPE Population Efficacy Results

HPV 6, 11, 16, or 18-Related	Quadrivalent HPV vaccine		Placebo		Efficacy (%)	95% CI
	N	Cases	N	Cases		
Persistent Infection	235	2*	233	45	96	83–100
Disease	235	0	233	6	100	12–100
CIN 1, 2, or 3	235	0	233	3	100	<0–100
Vulvar/vaginal neoplasias or genital warts	235	0	233	3	100	<0–100

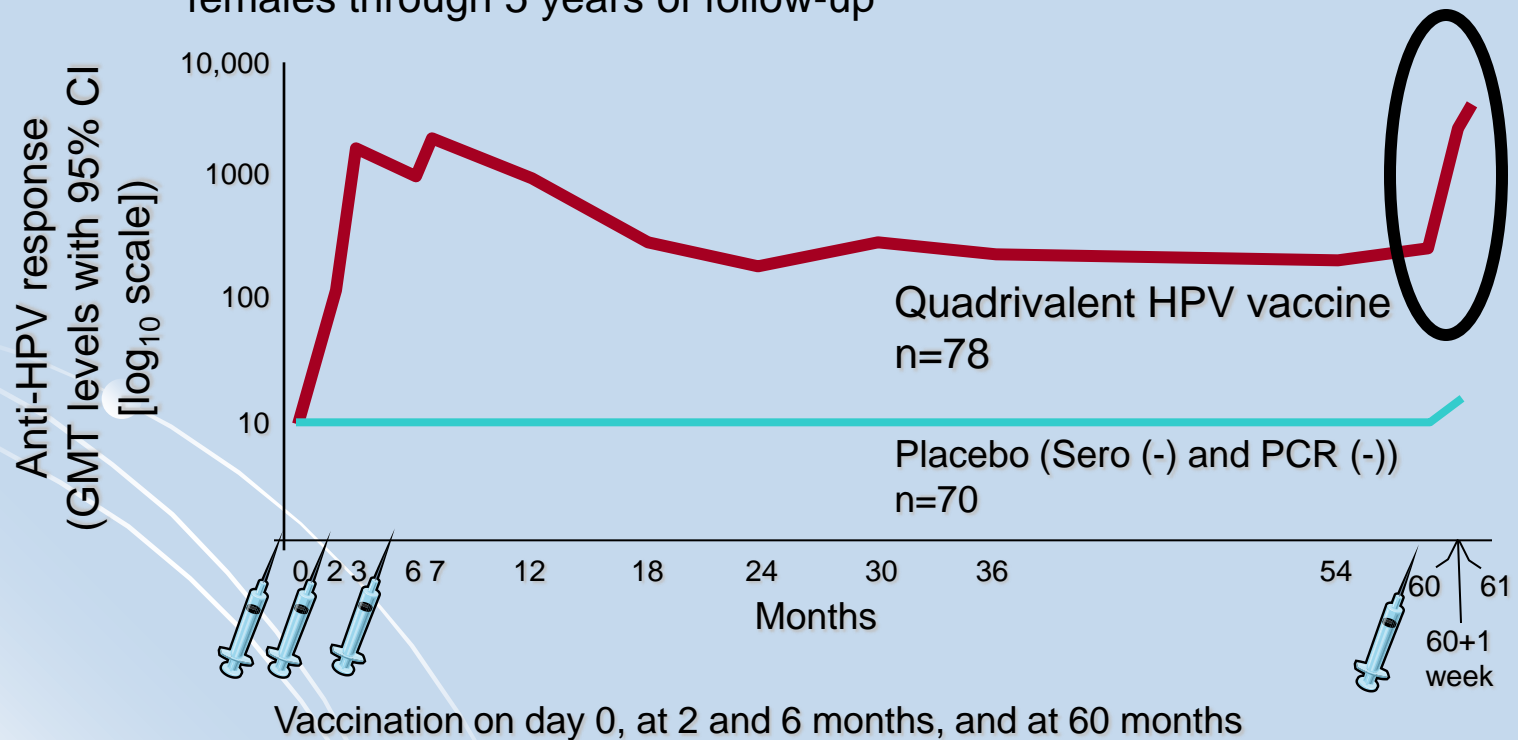
A total of 241 subjects were entered into the 5-year extension phase of Protocol 007.

*One case of confirmed persistent infection: HPV 18 DNA detected at months 12 and 18 only; not a case in the 5-year extension phase. One case of HPV 16 DNA detected at the last visit (month 36); not a case in the 5-year extension phase.

Antibody Response to Quadrivalent HPV vaccine Is Durable¹

Long-term Persistence of Anti-HPV 16 cLIA Responses*

Anti-human papillomavirus (HPV) 16 responses in 16- to 23-year-old females through 5 years of follow-up



*In subjects naïve to the relevant HPV type from day 1 through month 60.

1. Data on file, MSD.

Quadrivalent HPV Vaccine Induces Strong Immune Memory

- Vaccines containing Merck's Alum shown to induce immune memory and >20 year efficacy
- Study to demonstrate immune memory with Quadrivalent HPV Vaccine
 - Phase IIb efficacy study in young women
 - Give challenge dose of vaccine at Year 5
 - Observe for anamnestic responses

Impact of a Challenge Dose Per-Protocol Immunogenicity Population†

Study Interval	Challenge Dose		
	n	GMT	95% CI
HPV 16			
Month 7	78	3889	(3147, 4806)
Month 60	78	395	(303, 516)
Month 60+1wk	77	4532	(3115, 6593)
Month 61	78	6242	(4204, 9269)
HPV 18			
Month 7	82	756	(582, 980)
Month 60	82	44	(31, 62)
Month 60+1wk	79	1001	(720, 1391)
Month 61	82	1152	(841, 1578)

† Subjects who were naïve to the relevant vaccine HPV type at Day 1, remained free of infection with the relevant HPV type through Month 60, received a vaccination with HPV vaccine at Month 60, and had serology at Month 61.

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Primary Efficacy Results in women aged 24 -45

Combined Incidence of HPV 6/11/16/18-Related
Persistent Infection or Cervical/Vulvar/Vaginal Disease



Population	GARDASIL TM	Placebo	Efficacy	95% CI	P-value
All Subjects	4	41	91%	84, 98	<0.001
24- to 34-Year-Olds	2	24	92%	87, 99	<0.001
35- to 45-Year-Olds	2	17	89%	82, 99	<0.001

Pencegahan Kanker Leher Rahim yang paling ideal

- Vaksinasi HPV , paling ideal sebelum pernah melakukan hubungan seksual
- Tetap memeriksakan diri secara teratur, bila memungkinkan tes HPV dan tes Pap atau tes IVA
- Menghindari faktor risiko Kanker Leher Rahim
- Menjaga pola hidup sehat (olah raga, cukup istirahat dan makanan gizi seimbang)



TERIMA KASIH